

**REMARKS**

A Petition for Extension of Time is being concurrently filed with this Amendment. Thus, this Amendment is being timely filed.

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

***Status of the Claims***

Upon entry of the present Amendment, claims 1-16 and 18-30 are currently pending in the present application. The Office Action is final. Claims 1-9 and 18-29 are withdrawn from consideration as being directed to a non-elected invention. Claims 10 and 30 were amended and claim 17 cancelled without prejudice or disclaimer of the subject matter contained therein. No new matter has been added by way of the amendments. For instance, claim 10 has been amended to clarify the claimed invention and to include textual subject matter taken from claim 17, now cancelled. Additional support for claim 10 can be found on page 31, lines 22-25. Claim 30 was amended to correct a typographical error. Thus, no new matter has been added.

Also, no new issues have been raised by way of the present submission which presents the Examiner with the burden of additional search and/or consideration. Claim 10 was amended to incorporate the textual subject matter of claim 17, which was previously considered by the Examiner. Claim 10 was further amended to further clarify the invention and to remove issues under 35 U.S.C. § 112, second paragraph. Claim 30 was amended to correct a minor typographical error. Moreover, these amendments materially reduce issues and/or place the

application into better form for appeal. Thus, entry of the present Amendment is proper and thus respectfully requested.

Based upon the above considerations, entry of the present Amendment is respectfully requested.

***Claim Objection***

Claim 30 is objected to due to informalities. Applicants have amended claim 30, without prejudice or disclaimer of the subject matter contained therein, as the Examiner suggested. Applicants respectfully request reconsideration and withdrawal of the present objection.

***Issues Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness***

Claims 10-17 and 30 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

The Examiner asserts that claim 10 is vague and indefinite with regards to “tissue regenerating amount” of a neurotrophic factor and “a periodontically acceptable scaffold material.” The Examiner further asserts that the terms “regenerates,” “prevents” and “enhances” within claims 11-16 are relative terms which render the claims indefinite. Finally, the Examiner asserts that since claims 11-16 and 30 recite the limitation “therapeutically effective amount” in claim 10, there is insufficient antecedent basis for this limitation and therefore claim 30 is rendered indefinite with regards to what component of the transplant “is in the range of  $1 \times 10^{12}$  to  $1 \times 10^{-3}$  g.” Applicants respectfully traverse.

Although Applicants disagree, in order to further prosecution, Applicants have amended claim 10, without prejudice or disclaimer of the subject matter contained therein, to incorporate the textual subject matter of claim 17, now cancelled. The rejection to claim 17 is thus obviated.

Applicants also amended claim 10 to recite “...a therapeutically effective amount of a neurotrophic factor; and an absorbent material....” The amendment to claim 10 resolves the antecedent basis issue within the dependent claims, as well as define the scaffolding material as an absorbent material. Additional support for this amendment can be found on page 31, lines 22-25.

Applicants respectfully submit that the term “regenerates” means to reconstitute the cementum (claim 11), periodontal ligament (claim 12), alveolar bone (claim 13) and dental pulp (claim 15), which were lost due to periodontal disease.

Also, the term “prevents” in claim 14 implies that the cementum is regenerated on the dentin surface to prevent the epithelium invasion to the defect region.

Further, the term “enhances” in claim 16 means that a neurotrophic factor such as BDNF activates the regeneration cascade at the missing sites (defect regions of periodontal tissue), as BDNF is capable of increasing expression of bone-related proteins (*e.g.*, OPN, BMP-2, *etc.*) as well as vascularization.

Applicants respectfully submit that the terms “regenerates”, “prevents” and “enhances” must be interpreted in view of the specification. In this situation, the specification supports experiments which disclose after treatment with the composition of claim 10 increased levels of mRNA associated with increased tissue regeneration was observed. See alkali phosphatase (ALPase), bone morphogenetic protein-2, (BMP-2), bone morphogenetic protein-4 (BMP-4),

osteopontin (OPN), and osteoprotegerin (ORG) which were quantitated and discussed within the specification at page 38, line 15, to page 16, line 8. All expression of the above quantitated mRNA is associated with bone-related proteins. Applicants also note Figures 2A-D, 3A-B, 4A-D, 5A-C, 6A-B, 7A-B and 8A-B of the specification. Additionally, Figures 9A-B support the prevention of gingival epithelium along the dental root surface.

Further, the term “regeneration” is defined in the specification in paragraph [0044] of the specification. Additionally, further definitions are provided in paragraphs [0046] and [0047] of the specification.

Concerning the Examiner’s assertion that claim 30 is vague and indefinite in its recitation of an effective amount per “defect of furcation,” Applicants submit that the term “furcation” is known within the art. Applicants provide Exhibit 1 (Ramfjord, S.P., and Ash, Jr., M. M., *Treatment of Furcation Involvement*, Periodontology and Periodontics, W. B. Saunders Company, page 666 (1979)) for the Examiner’s consideration. Exhibit 1 describes “The extensions of periodontal pockets that may occur between the roots of multirooted teeth are called furcation involvements.” Therefore, a furcation may be understood as a periodontal tissue defect between the roots of multirooted teeth.

Regarding an effective amount per “defect of furcation,” since forms of such a defect vary greatly according to such factors as individual subjects, regions and the degree of progressive stages, a therapeutically required amount varies accordingly. As for an amount of BDNF, for example, an effective amount may be in the range of  $1 \times 10^{-12}$  g to  $1 \times 10^{-3}$  g per 1 ml of carrier material (or an equivalent amount thereof).

Therefore based on the present amendments and the comments above, Applicants submit that the claims particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants respectfully request reconsideration and withdrawal of the present rejection.

***Issue Under 35 U.S.C. § 102(b), Anticipation***

Claims 10-16 stand rejected under 35 U.S.C. § 102(b) as anticipated by Kirker-Head, Advanced Drug Delivery Reviews, 43:65-92, 2000 (hereinafter “Kirker-Head”). See page 4-5 of the Office Action dated November 17, 2008 (hereinafter “Office Action”). Applicants respectfully traverse.

Although Applicants do not agree with the Examiner’s assertions, in order to advance prosecution, claim 10 has been amended, without prejudice or disclaimer of the subject matter contained therein, to incorporate the textual subject matter of non-rejected claim 17, now cancelled. Since Kirker-Head is silent regarding a periodontal transplant which comprises a therapeutically effective amount of a neurotrophic factor, wherein the neurotrophic factor is selected from the group consisting of a brain-derived neurotrophic factor, a nerve growth factor, neurotrophin-3, and neurotrophin-4/5, it does not teach the present invention.

Because “a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference,” the cited Kirker-Head reference cannot be a basis for a rejection under § 102(b). *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicants respectfully request reconsideration and withdrawal of the present rejection.

***Issue Under 35 U.S.C. § 103(a), Obviousness***

Claims 17 and 30 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Kirker-Head as applied to claims 10-16, further in view of Tsuboi *et al.*, J. Dent. Res., Vol. 80, No. 3, pp. 881-886 (2001) (hereinafter “Tsuboi”), Kurihara *et al.*, J. Periodontol., Vol. 74, No. 1, pp. 76-84, (2003) (hereinafter “Kurihara”) and Harada *et al.*, Arch. Hisol. Cytol., Vol. 66, No. 2, pp. 183-194, (2003) (hereinafter “Harada”).

Applicants respectfully traverse. Claim 17 has been cancelled, thus obviating this rejection with regard to claim 17. However, in as much as the rejection may be applied to amended claim 10, which incorporates claim 17 herein, the following remarks are submitted.

*Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. But before the Examiner can utilize these guidelines, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*; *supra*. To reject a claim based on the above mentioned guidelines, the Examiner must resolve the *Graham* factual inquiries. MPEP §2143.

If the Examiner resolves the *Graham* factual inquiries, then the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 sets forth the rationales that were established in *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Applicants respectfully submit that the Examiner has not appropriately resolved the *Graham* factors, including the factors of determining the scope and content of the prior art and ascertaining the differences between the prior art and the claims that are at issue. Based on the following, Applicants maintain that the above mentioned *Graham* factors actually reside in Applicants' favor. Additionally, Applicants submit that since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides for combining the cited references is improper.

Applicants respectfully submit that the presently claimed invention is distinct from and unobvious over Kirker-Head combined with Tsuboi, Kurihara and Harada.

As the Examiner correctly states, the Kirker-Head reference does not teach a transplant comprising BDNF. Moreover, the Kirker-Head reference merely discloses effects of BMP-2 on skeletal tissue formation, and is silent regarding periodontal tissue regeneration. Therefore, Applicants submit that it is not obvious for the skilled artisan to combine the Kirker-Head reference with the above cited references indicating effects of BDNF on periodontal tissue.

Further, for discussion of regeneration of periodontal tissues, Applicants note that that periodontal tissues are composed of gingiva, alveolar bone, periodontal ligament (periodontal membrane), cementum, dental pulp, etc. (See paragraph [0002] of the present specification). In view of this, Applicants respectfully submit that Tsuboi, Kurihara and Harada do not suggest regeneration of periodontal tissues including both soft and hard tissues.

*Differences between the prior art and the present invention*

The Tsuboi reference discloses expression of neurotrophins in MPL (mouse periodontal ligament cell line) and that neurotrophins enhance proliferation of MPL. From the disclosure in Tsuboi, it is not expected that neurotrophins such as BDNF are effective in regenerating periodontal tissues including periodontal ligament as well as cementum and alveolar bone.

With regards to Kurihara, this reference appears to indicate potential contribution of neurotrophins to the regeneration of periodontal tissues, from the *in vitro* data on mRNA expressions of bone-related proteins known to be involved in hard tissue regeneration, such as ALPase, OPN and BMP-2. Nevertheless, Applicants submit that regeneration of hard tissues alone does not achieve the desired regeneration of healthy periodontal tissues, as these tissues are composed of not only alveolar bone but also periodontal ligament and cementum. For example, for the Examiner's consideration Applicants provide Exhibit 2 (Wikesjö *et al.*, "Periodontal Repair in Dogs: Effect of rhBMP-2 Concentration on Regeneration of Alveolar Bone and Periodontal Attachment," J. Clin. Periodontol. Vol. 26, pp. 392-400 (1999)). Applicants refer to Exhibit 2 which reports *in vivo* data using BMP-2. Exhibit 2 reports the functions of BMP-2, that BMP-2 was capable of regenerating alveolar bone but was not effective in regenerating cementum or periodontal ligament, and that ankylosis (bony attachment, which may become a healing aberration) was observed in teeth receiving BMP-2.

Concerning the Harada reference, it merely suggests involvement of BDNF in the regeneration process of periodontal nerves (Reffini endings).

The present invention

In contrast, the inventors of the present application have shown, based on *in vitro* data, that a neurotrophic factor such as BDNF enhances generation of collagen in soft tissues, a component of periodontal ligament (See Example 1 within the present specification). The inventors have further shown, based on *in vivo* data, that alveolar bone as well as cementum and periodontal ligament are regenerated by a neurotrophic factor such as BDNF (See Example 2 of the present specification).

Applicants submit that none of the above cited references disclose that neurotrophic factors (neurotrophins) including HDNF are effective in regenerating periodontal tissues comprising both hard tissues and soft tissues. The present application is the first to demonstrate that a neurotrophic factor is effective in the regeneration of healthy periodontal tissues, composed of both hard tissues, such as alveolar bone and cementum, and soft tissues such as periodontal ligament.

Applicants respectfully disagree with the Examiner that the present invention would be obvious to the skilled artisan. In view of the above, it submitted that the present invention as claimed is suitably distinguished over the combination of references cited.

In light of the above presently amended claims and remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the cited references that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the Kirker-Head reference is incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Also, Tsuboi, Kurihara and Harada fail to compensate for or teach the deficiencies in Kirker-Head. Therefore, the combinations of Kirker-Head with the

Tsuboi, Kurihara and Harada references do not arrive at the present invention. Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established for remaining claim 30.

As such, the instant invention of amended claim 10 or claim 30 is not obvious over Kirker-Head combined with Tsuboi, Kurihara and Harada. Applicants respectfully request reconsideration and subsequent withdrawal of the present rejection.

**CONCLUSION**

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case.

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By  #47874

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Attachments: Exhibit 1: Ramfjord, S.P., and Ash, Jr., M. M., "*Treatment of Furcation Involvement*," Periodontology and Periodontics, W. B. Saunders Company, page 666 (1979).

Exhibit 2: Wikesjö et al., "*Periodontal Repair in Dogs: Effect of rhBMP-2 Concentration on Regeneration of Alveolar Bone and Periodontal Attachment*," J. Clin. Periodontol. Vol. 26, pp. 392-400 (1999).